Pancreatic Islet Transplantation—Experimental Experience and Clinical Potential

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New theoretic developments in transplantation biology indicate that it is possible to reduce the immunogenicity of a graft by removing antigen-presenting cells (leukocytes) from the tissue before grafting. Also becoming apparent is that cellular replacement therapy, the grafting of cells or clusters of cells, can be used to treat metabolic disorders such as type I diabetes mellitus. In the past, immune rejection has been a major problem and long-term patient immunosuppression is not warranted in patients with type I diabetes. Results of studies in animals show that under defined genetic conditions, mature islet tissue or immature fetal proislets may be transplanted across major histocompatibility barriers without a requirement for recipient immunosuppression. We are now ready to commence applying this technology clinically. These developments will initially be very experimental and limited in scope but should accelerate as data emerge from the initial trials.

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Recently there have been two new developments in transplantation biology. The first is the return of the passenger leukocyte concept, although not in its original form that saw the mobile lymphoid cell as a vehicle for transporting transplantation antigen to a regional lymph node where it initiated an immune response, resulting in rejection of the grafted tissue. The new concept is somewhat more sophisticated. We now recognize that the transplantation antigen per se is not the major barrier to tissue grafting. This is because two signals, antigen and a source of costimulator activity, are required to trigger the antigen-specific lymphocyte response. Antigen-binding by the T-cell receptor provides one signal, and costimulator activity is the second signal. Interleukin 1 possesses costimulator activity, but may not be the only molecule that expresses such activity. Cells that provide a source of costimulator activity are said to express the S^+ phenotype, and such cells (stimulator cells) present alloantigen in a highly immunogeneic form to responsive T cells because they provide both signals required for T-cell activation. Stimulator cells are cells of lymphoreticular origin, possibly tissue dendritic cells; we cannot be sure that these are the only potential stimulator cells. The S^+ cells carried in a graft provide the major source of tissue immunogenicity, and it is for this reason that passenger leukocytes play such an important role in activating the allograft response.[1]

The second development is the use of cellular replacement therapy for the treatment of metabolic defects. An example of this approach is the use of either isolated islet cells, islets or proislets as a source of insulin-producing tissue that can be transplanted for the treatment of diabetes. This represents a shift away from the concept of organ transplantation as a treatment for this disorder, and provides an ideal model with which to test the concept that it is possible to reduce tissue immunogenicity by removing passenger leukocytes (S^+ cells) before transplantation.

In this article, I discuss experience with this approach in using islets, fetal pancreas and fetal proislet transplantation as a treatment for insulin-dependent diabetes mellitus in rodent systems and the potential for applying this technology clinically.

Syngeneic Islet Transplantation

The early work of Lacy's group in St Louis on isolating pancreatic islets and studying their physiology led to the notion that transplantation of this tissue could be used to correct the metabolic defect of insulin-dependent diabetes.[2] Initial studies using syngeneic transplantation involved implanting islet tissue into the liver, a site considered appropriate in view of the action of insulin in this organ. More recent studies have shown, however, that the tissue functions equally well when transplanted to the renal capsule of recipient animals.[3] It is likely that the good results seen in relation to kidney capsule transplantation merely reflect the appropriateness of this site for tissue transplantation. While it is probably beneficial to

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have the insulin delivered into the portal circulation, it would appear that implanting islets into the liver itself is not the most efficient form of transplantation. Transplanted islet tissue has also been shown to prevent development of the vascular complications of diabetes.[4]

The site of implantation is important when considering islet grafting as a treatment for diabetes. Islet tissue can be implanted at an intramuscular site where it becomes revascularized and granulated β-cells develop. This site is attractive in terms of access. However, both our group using transplanted fetal pancreas (unpublished results) and Lacy's group working with adult islets[2] found that tissue could be transplanted to an intramuscular site where granulated β cells developed, but in neither case would such transplants correct the metabolic defect. The same or even a smaller amount of tissue transplanted to the renal capsule did reverse the diabetes in these animals.[3,5] We have evaluated a number of different transplantation sites in pigs by comparing the survival of thyroid autografts transplanted subcutaneously, intramuscularly, beneath the renal capsule and in an omental pocket (C. J. Simeonovic, PhD; D. P. Dahll, MD, PhD; J. D. Wilson, MD, "A Comparative Study of Transplant Sites for Endocrine Tissue Transplantation in the Pancreas," submitted for publication). Best results were obtained with the renal capsule and the omental site. The omentum offers the advantage that its vascular bed drains into the portal circulation, and recently Yasunami and co-workers have shown that tissue transplanted in the omentum will reverse diabetes in rats.[6]

Allogeneic Islet Transplantation

From a physiologic standpoint, islet transplantation provides an attractive and effective approach to treating patients who have insulin-dependent diabetes. In the past, immune rejection has been a major problem and long-term patient immunosuppression is not warranted in the case of patients with diabetes. The demonstration, however, that the immunogenicity of tissues can be reduced by organ culture before transplantation has revolutionized our approach to this problem.[1] It allows allotransplantation of islet tissue without a need for immunosuppression of the recipient.

The organ culture technique was initially developed using thyroid and parathyroid transplantation.[7] Early attempts to apply this technique to the treatment of pancreatic islets before transplantation were frustrated by technical difficulties. The loss of tissue immunogenicity during culture is an oxygen-dependent phenomenon thought to result from the sensitivity of leukocytes to oxygen. Single pancreatic islets isolated from adult pancreata are extremely sensitive to oxygen and rapidly degenerate when cultured in an oxygen-rich atmosphere. This toxicity problem can be overcome by allowing groups of about 50 islets to aggregate and fuse together. Islet clusters are more resistant to oxygen toxicity and can be successfully allotransplanted in mice after one week of culture under these conditions.[8]

Following culture, islet allografts of seven islet clusters—that is, about 350 islets—have been shown to reverse streptozocin-induced diabetes in mice. Blood sugar levels of transplanted animals rapidly returned to normal, the animals became aglycosuric and they responded normally to the administration of glucose.[9] Uncultured islets, on the other hand, temporarily reverse diabetes, but the recipient animals return to a diabetic state within four weeks of transplantation.

TABLE 1.—*Transplantation of Cultured Islets Between Defined Mouse Strains and to Members of an Outbred (O/B) Mouse Colony*

Strain Combination	Donor Pretreatment	Number Transplanted	Survival N	Survival (%)
BALB/c+BALB/c	None	14	14	(100)
BALB/c+CBA	None	20	20	(100)
BALB/c+O/B	None	22	5	(23)
BALB/c+O/B	Donors treated with cyclophosphamide (300 mg/kg) on days −4 and −2 and tissue harvested on day 0	16	9	(56)

More recently, we have also seen a synergism between cyclophosphamide pretreatment of a donor and organ culture of the islet tissue for one week in an oxygen-rich atmosphere. Cyclophosphamide treatment of donor animals before the harvest of tissue causes a profound decrease in the capacity of spleen cells to stimulate allogeneic T cells in culture.[7] This treatment has reduced the immunogenicity of thyroid allografts when administered four and two days before harvesting tissues for grafting. The drug is myelotoxic and has recently been shown to reduce the level of dendritic cells in tissues such as the kidney.[10] We have used this procedure to examine the feasibility of islet transplanting without immunosuppression to members of an outbred mouse population (Table 1). These studies were carried out by following the survival of cultured (BALB/c) islet clusters after transplanting to normal nonimmunosuppressed mice from either inbred colonies or from a colony of randomly bred mice (Table 1). Organ culture alone in an oxygen-rich atmosphere resulted in 100% allograft acceptance across the defined strain combination (BALB/c to CBA), but resulted in only 23% survival when the same tissue was transplanted in outbred animals. When organ culture was combined with cyclophosphamide pretreatment of the BALB/c donors, however, survival in the outbred population increased significantly to 56%. These results show the feasibility of allogeneic islet transplantation, without recipient immunosuppression, in an outbred animal population. They also emphasize the problems associated with genetic variability within the recipient populations. Such problems would have to be expected in a clinical situation.

Lacy's group achieved similar results in rats, but in their initial studies islets were not cultured in 95% oxygen, and allograft acceptance was only achieved when recipient animals were treated with a single dose of antilymphocytic serum at the time of transplantation.[11]

Tissue Immunogenicity

Progress has been made in understanding the mechanism whereby graft pretreatment before culture reduces tissue immunogenicity. Faustman and associates showed a dependence of islet immunogenicity on the presence of Ia-positive cells in transplanted tissue by achieving allograft survival following anti-Ia serum and complement treatment of the donor tissue before transplantation.[12] Ia antigen recognition is not an absolute requirement, however. Morrow and colleagues have shown that islet allograft rejection occurs when there is I-region compatibility between donor and recipient.[13] The fact

that rejection is dependent on the presence of an Ia-positive cell in the tissues is consistent with the notion that the stimulator cell (S^+) carries Ia antigen on its surface, but that recognizing Ia antigen is not a requirement for T-cell activation.

While the organ culture procedure reduces tissue immunogenicity, it does not alter antigen expression on the surface of a graft. The tissue is antigenic but weakly immunogenic. In the immediate posttransplant period, the tissue is in a metastable state, and the graft is acutely rejected when the recipient is challenged with living leukocytes of donor origin.[14] Procedures have now been developed that allow a graft to be stabilized following transplantation (see Development of Specific Tolerance below). The experimental investigation of cell populations to determine which cell types express the S^+ phenotype, as determined by their capacity to trigger graft rejection, have shown peritoneal cells to be active. B cells are inactive,[15] providing further evidence that expression of the Ia antigen is not a sufficient requirement for expression of the S^+ phenotype.[16] T cells can also trigger rejection, but only when they are used in a situation wherein the T cell can become activated in the host. This phenomenon probably reflects the fact that costimulator activity is a product of activated T cells. It is important to emphasize that more than one type of leukocyte can be involved in stimulating the specific allograft response.

Xenogeneic Islet Transplantation

Islet xenografts between discordant species (distantly related species) are rapidly rejected, often in a hyperacute manner. Xenografts of fish islets to rats, chick embryo islets to rats or mice and neonatal rabbit and calf islets to rats are all rejected within four days.[17] Xenografts between concordant (closely related) species have a rejection time similar to allografts. Transplants from rats to mice are rejected in two to five days.[17,18] If antilymphocyte serum is given at the time of transplantation, survival is prolonged to 10 to 12 days.[18] Islets used for these studies were obtained from crude pancreatic digests and were contaminated with nonislet tissue. A more carefully purified rat islet preparation survived for seven days in diabetic mice and up to eight weeks in immunosuppressed mice if large multiple doses of antilymphocyte serum were given.[19,20] Highly purified preparations of rat islets obtained by careful handpicking of pancreatic digests survived for 10 to 14 days in normal mice and from 15 to 82 days in mice that received one dose of antilymphocyte serum.[21] Cultivating such tissue in 95% oxygen extends the graft survival in normal mice to between 20 and more than 70 days.[22] Similarly, the survival of purified neonatal rat islets in mice was extensively prolonged, with rejection times of between 9 and 49 days.[23]

We have not been able to achieve long-term function of rat islet xenografts in diabetic mice (greater than 50 days) if the islets are taken from cyclophosphamide-pretreated donors and are cultured for 14 days in 95% oxygen before grafting to recipients that receive cyclosporine for the first 14 days posttransplantation (K. Lafferty, PhD, unpublished data, December 1983). Further studies are required to determine the minimal conditions needed to obtain such long-term xenograft survival. The fact that xenografts can be established in animals receiving minimal immunosuppression is encouraging, however.

Transplantation of Fetal Tissue

Pancreatic islet transplantation presents an attractive approach to treating patients with insulin-dependent diabetes, although attempts to isolate large numbers of islets from the human pancreas have been hindered by the very fibrous texture of adult tissue. Recent advances in the preparation of islets from large animals, however, forecast the potential feasibility of developing technical procedures for the large-scale isolation of human islets.[24] For practical reasons, fetal pancreas is the tissue of choice for clinical islet transplantation at the present time.

Isografts of a single fetal pancreas can reverse diabetes in rodents. The fetal pancreas is more immunogenic than adult islets, however. Allografts of fetal mouse pancreata that had been cultured for up to ten days before transplantation are acutely rejected when transplanted from BALB/c to CBA mice.[25] The rejection process is well established within two weeks of transplantation and, by four weeks, only scar tissue and scattered mononuclear cells remain at the graft site. This difference in behavior between adult islets and fetal pancreas is attributed to a large lymphoid component associated with the latter. This lymphoid tissue is not actually in the pancreas itself, but appears to represent developing lymph nodes associated with the mesentery that surrounds the rather diffuse rodent pancreas in situ. Large numbers of Ia-positive (dendritic?) cells have also been observed throughout fetal human pancreas.[26] We have observed lymphoid remnants in association with the ten-day cultured fetal pancreas, however, and it is likely that this residual lymphoid tissue triggers the rejection process. It is possible to successfully transplant fetal pancreata to nonimmunosuppressed allogeneic recipients following a longer (17- to 20-day) period of organ culture. However, the functional capacity of this tissue decreases as the culture period is increased.[5]

Fetal proislets, obtained by collagenase digestion and further culture of the fetal pancreas digest, provide a more promising tissue for the purpose of clinical transplantation in treating diabetes. Fetal mouse proislets are not highly immunogenic and can be successfully allotransplanted across a major histocompatibility barrier. At four weeks posttransplantation, about 50% of the proislet allografts contain differentiated islet tissue without any evidence of mononuclear cell infiltration. Remaining grafts were rejected.[27]

Fetal proislets develop into mature islets following transplantation. Histologic examination of freshly digested fetal pancreas shows the presence of differentiated acinar tissue, considerably disrupted after the collagenase treatment, and a small amount of undifferentiated tissue. After another four days in culture (atmosphere 10% of carbon dioxide in air), the digest units consist of discrete ovoid cellular aggregates containing undifferentiated cells, some tubular components, connective tissue and occasional peripheral regions of cellular organization that resemble endocrine tissue.[28] At this stage, the tissue shows only occasional insulin- and glucagon-containing cells when stained with immunoperoxidase-labeled antibody. After isotransplantation, however, the proislets developed into islets with normal morphology that stained for both insulin and glucagon; small numbers of dendritelike somatostatin-containing cells have also been observed in islets formed following proislet transplantation (K. Lafferty, PhD, unpublished data, November 1984).

TABLE 2.—*Reversal of Diabetes (Streptozocin-Induced) in CBA Mice Transplanted With Proislets Obtained From Varying Numbers of Fetal CBA Donors (17 Days' Gestation).*

Pancreas Equivalents Transplanted	Proportion Normoglycemic	Recovery Time (d)
8	6/7	20 - 93
6	6/6	12 - 76
4	8/8	8 - 62
2	4/7*	14 - 62

*Animals in this group have so far been observed for a maximum of 62 days.

Fetal proislets will function to reverse streptozocin-induced diabetes. Table 2 shows the results obtained when tissue from eight-, six-, four- and two-CBA fetal mouse donors was transplanted to the renal capsule of syngeneic recipients. Tissue from two fetal donors has the capacity to reverse diabetes, and animals that have reversed or become normoglycemic show a normal response to the oral administration of glucose.[9] The remaining three animals in this group, which have not reversed by 62 days, are still under investigation. We have preliminary evidence that tissue from one fetal donor will eventually render diabetic animals normoglycemic. It can take from four to six months, however, for this tissue to effectively control the diabetic condition. Human fetal proislets have been prepared by collagenase digestion of tissue obtained from aborted fetuses (12 to 16 weeks' gestation). Granulated β-cells develop when this tissue is transplanted to the kidney capsule of athymic mice. The development of this tissue is slow, and well-granulated β-cells are not usually seen until ten weeks or more after transplantation (K. Lafferty, PhD, unpublished data, November 1982). Fetal proislets appear, therefore, to be the most appropriate tissue for use in clinical islet transplantation.

Development of Specific Tolerance

Cultured allografts of both thyroid and pancreatic islet tissue carry recognizable antigen and can be promptly rejected when recipient animals are challenged with leukocytes of donor origin at the time of transplantation. However, animals carrying allografts for a prolonged period (equal to or greater than 100 days) become progressively more resistant to challenge with donor cells.[29] In the case of thyroid, we have found that grafted tissue retains antigen and that this adaptation of the graft to its host results from the development of tolerance in an adult recipient.[30] We argued that this phenomenon might develop as a result of slow leakage of free antigen into the immune system of the recipient, possibly inducing tolerance in a manner akin to active enhancement. Support for this notion has come from the pancreatic islet system. When transplanted animals are injected with ultraviolet-wave-killed donor spleen cells—a source of alloantigen on nonstimulating cells—around 30 days posttransplantation, graft rejection is not stimulated. Viable donor cells administered at this time promptly activate a rejection reaction. That is, the ultraviolet-irradiated cells were subsequently challenged with viable donor spleen cells and the allografts were not rejected. The ultraviolet-irradiated cells, which provide a source of antigen alone, have stimulated the development of tolerance in grafted animals. The specificity of this tolerance was shown by the fact that animals would accept an uncultured thyroid allograft of donor origin but would reject a third-party thyroid grafted to the same recipient at the same time. We have also shown, in the case of both thyroid- and islet-transplanted animals, that this phenomenon is not a deletion form of tolerance. Lymphocytes from "tolerant" animals respond normally to donor alloantigen in vitro.[14] Faustman and co-workers suggested that such unresponsiveness may result from the action of suppressor cells.[31]

In a recent publication, Lau and associates showed that pretreating rats with ultraviolet-irradiated blood from the putative donor strain would induce a stage of specific tolerance and allow prolonged acceptance and function of an untreated islet allograft. This tissue tolerance was also specific; animals transplanted with islets from a third-party donor rejected such grafts acutely, as did animals transplanted with islets in the absence of recipient pretreatment.[32]

The independent confimation by a number of laboratories that tissue tolerance can be induced in adult animals is one of the most exciting recent developments in transplantation biology. Our own experience in this area indicates that there may be a very delicate balance between inducing either tolerance or immunity following treatment of animals with ultraviolet-irradiated cells. Much work must be done to analyze the cellular and molecular basis of this phenomenon, and it would be premature to see it as the answer to the problems associated with the use of immunosuppression in clinical transplantation. It is unquestionably a fruitful area for further research, however.

Clinical Potential

As yet, there is only one published report of this approach to the treatment of diabetes in humans.[33] This report comes from Farkas and Karacsonyi working in Hungary who reported the results of infusing cultured human fetal proislet tissue into the liver of recipients with diabetes via the umbilical vein.[33] Both patients, who had severe retinopathy, were infused with tissue derived from two fetal donors that is ABO compatible with the recipient. Both recipients were immunosuppressed with steroids and azathioprine for seven to eight months following transplantation.

In both cases there was a significant drop in the daily insulin requirement, although neither patient became independent of insulin. Basal serum C-peptide levels were initially undetectable in one case and low (0.6 ng per ml) in the other. By eight to ten months posttransplantation, both patients had significant C-peptide levels (1.9 and 1.2 ng per ml, respectively), and at ten months following transplantation both patients showed a strong C-peptide response to oral glucose challenge. Progression of retinopathy was arrested in both cases.

This first report is encouraging. This new technology has begun to be applied to the clinical situation and it is hoped that this is the first step towards the development of cellular replacement therapy for the treatment of type I diabetes.

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